

EXHIBIT 42



Active warming systems to maintain perioperative normothermia in hip replacement surgery: a therapeutic aid or a vector of infection?

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Received 13 March 2009; accepted 4 June 2009

Available online 31 July 2009

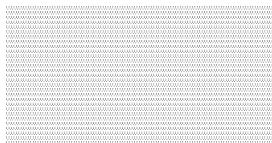
KEYWORDS

Bair Hugger system;
Nosocomial infection;
Orthopaedic surgery;
Thermoregulation

Summary Various reliable body heat-regulating systems have been designed and developed with the aim of maintaining an adequate body temperature in the course of major surgery. This is crucial to avoid the onset of potentially severe complications that are especially serious in elderly and debilitated subjects. Among these systems, the Bair Hugger blanket has demonstrated excellent efficacy. However, some reports in the literature have suggested that the use of such devices can increase the risk of nosocomial infections, particularly surgical wound infections. The aim of this study was to assess the risk of contamination of the surgical site correlated to the use of the Bair Hugger blanket during hip replacement surgery. To this end, the level of bacterial contamination of the air in the operating theatre was quantified with and without the use of the Bair Hugger, during the course of 30 total non-cemented hip implants performed in patients with osteoarthritis. Sampling was done both in the empty theatre and during surgical procedures, in different zones around the operating table and on the patient's body surface. Statistical analysis of the results demonstrated that the Bair Hugger system does not pose a real risk for nosocomial infections, whereas it does offer the advantage of preventing the potentially very severe consequences of hypothermia during major orthopaedic surgery. In addition, monitoring patients over the six months following the

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operation allowed us to exclude a later manifestation of a nosocomial infection.

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Introduction

A number of studies have demonstrated that a drop in body temperature, especially during major surgery, can cause potentially dangerous complications, particularly in the elderly and debilitated, or in those with pre-existing disease.^{1,2} Nosocomial infections are a particular problem, adversely affecting the postoperative course in terms of patient morbidity, longer hospital stay and higher associated costs for the healthcare facility.^{3–7}

To guarantee the maintenance of an adequate body temperature, a number of different regulation systems with proven efficacy have been designed and developed.^{8,9} Among these is the Bair Hugger system (Augustine Medical Inc., Eden Prairie, MN, USA), that consists of a temperature management unit comprising a heat generator, a blower to circulate the heated air and a temperature control system equipped with various sensors. This unit is connected by a rubber tube to a blanket that is heated by circulating warm air, thus maintaining the surface temperature of the body underneath it within a physiological range.^{10,11}

Some reports in the literature, however, have suggested that such body-warming devices could themselves pose a risk factor for perioperative nosocomial infections, especially at the surgical wound site.^{12–16} The aim of this study was to assess the infective risk associated with the use of such devices during hip replacement surgery. We studied the levels of bacterial contamination in the operating theatre potentially associated with the use of the Bair Hugger.

Methods

To assess the infective risk potentially correlated with the use of the Bair Hugger body-warming system, the levels of bacterial contamination present in the air in the operating theatre were monitored with and without the use of the forced-air warming blanket.^{17,18}

The air sampler used was an Active Surface Air System (SAS; Aquaria, s.r.l, Italy), a single plate sampling system that directs a constant flow of air on to an agar plate, and which meets the ISO

14698-1 standard. The efficacy of the device is evaluated on the basis of the cut-off size (d_{50}), i.e. the minimum diameter of the particles selected by the sampler. Pasquarella *et al.*, in a recent review, reported the different cut-off size of some air samplers as ranging from 0.58 µm (Andersen Cascade Impactor, stage n.6) to 7.5 µm (Reuter Centrifugal Sampler).¹⁹ The SAS has a d_{50} of 1.5 µm, implying a good level of efficacy; it is particularly suitable for studying air where there may be low concentrations of organisms, such as in hospital environments.^{19–22} Moreover, despite the greater efficacy of the Andersen sampler, Morris *et al.* recommended the use of the SAS device because of its being so practical and reliable when used in epidemiological studies and during outbreak investigations in hospital environments.²³

The air was blown at a flow rate of about 90 L/min onto 55 mm Petri dishes containing Plate Count Agar culture medium to quantify the total bacterial load; Mannitol salt agar (MSA), Wurtz and Sabouraud agars (all agars supplied by Biolife Italiana s.r.l, Milan, Italy) to make a qualitative assessment of any organisms found. After sampling, the plates were incubated at 36 °C in air for 48 h before counting and identifying any potentially pathogenic micro-organisms.

The bacterial counts were expressed as cfu/m³ (colony-forming units per square metre of air).

Sampling was done during total non-cemented hip implantations performed on 30 female patients with osteoarthritis, with a mean age of 64 years (range: 58–71). All procedures were performed at the Bari University Hospital, Italy. In 20 of the subjects, a Bair Hugger blanket was placed on the operative couch, and used for an average period of about 90 min. As suggested by Huang *et al.*, sampling was done for all the procedures, both at rest, when the theatres were empty and not being used, and under operational conditions, in three different points (A1, A2 and A3) around the operating table, as shown in Figure 1 and at two different times (prior to patient placement on the table, and at the start of the procedure).¹³

In the 20 cases in which the Bair Hugger was used, sampling was also carried out during the course of the operating procedures. For these subjects, environmental sampling was done in

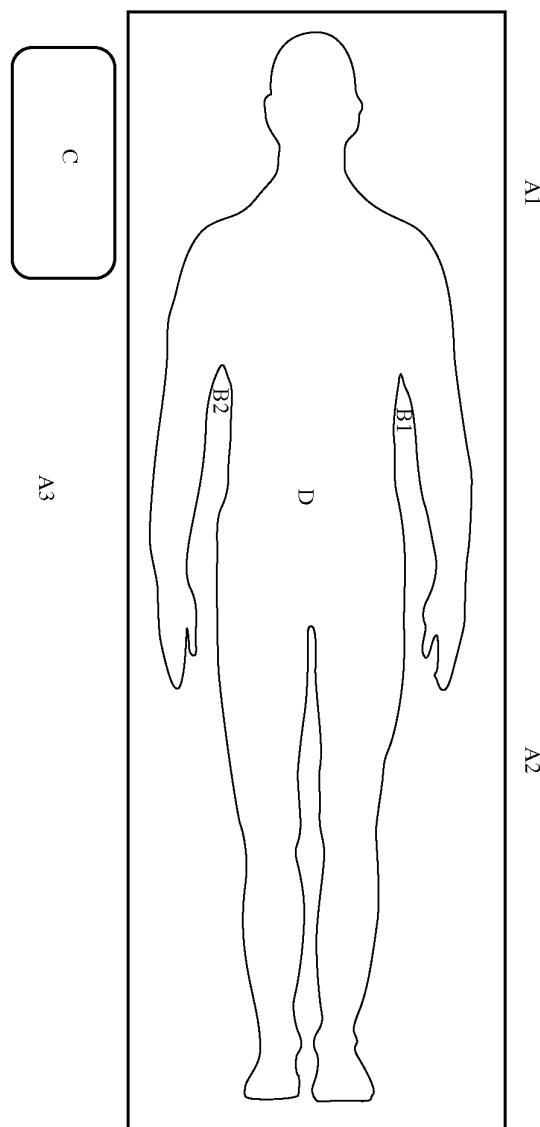


Figure 1 Air sampling points. (Redrawn from Huang et al.¹³ by kind permission.)

the zones around the axillae, where the air emerged (B1 and B2, Figure 1) and in the zone around the blower (tube and heating unit filter). Samples were also taken from the patient using sterile buffers on the skin surface to be incised, before disinfecting the skin, and in the same way on the same area at the end of the procedure.

To reveal any significant variations among the three sampling points of the operative site (A1, A2, A3, Figure 1) analysis of variance was performed; the alpha level of significance was set at $P < 0.05$. Statistical analysis of the environmental samples was done using the SAS statistical software package (SAS Institute Inc., Carolina, USA). All patients were

monitored for a further six months to check for late onset of nosocomial infection.

Results

Under the at-rest conditions in the empty theatres, no significant differences were observed among the mean values of the bacterial loads measured at the three different points around the operative site ($A1 = 17.8 \pm 14.5 \text{ cfu}/\text{m}^3$; $A2 = 19.4 \pm 17.5 \text{ cfu}/\text{m}^3$; $A3 = 19.2 \pm 17.7 \text{ cfu}/\text{m}^3$; $F = 0.09$, $P > 0.05$). In all three points, however, a significant increase in the mean bacterial load was observed under operational conditions, immediately after placing the patient on the operating table ($A1 = 79.2 \pm 52.2 \text{ cfu}/\text{m}^3$, $F = 38.54$, $P < 0.001$; $A2 = 61.2 \pm 38.8 \text{ cfu}/\text{m}^3$, $F = 28.92$, $P < 0.001$; $A3 = 69.1 \pm 56.8 \text{ cfu}/\text{m}^3$, $F = 21.09$, $P < 0.001$; Figure 1).

In the 20 procedures in which the Bair Hugger was used, the mean bacterial load values were significantly increased in the three points compared with the at-rest conditions ($A1 = 41.7 \pm 28.1 \text{ cfu}/\text{m}^3$, $F = 15.6$, $P < 0.001$; $A2 = 42.2 \pm 28.6 \text{ cfu}/\text{m}^3$, $F = 12.2$, $P = 0.001$; $A3 = 42.3 \pm 28.2 \text{ cfu}/\text{m}^3$, $F = 12.62$, $P < 0.001$; Figure 1). However, in point A1 there was a significant reduction of the mean bacterial load values between the moment in which the patient was placed on the operating table and after the use of the Bair Hugger ($F = 8.62$, $P < 0.05$; Figure 2).

The mean bacterial load recorded during the 20 procedures in which the full body forced-air warming system was employed was $36.8 \pm 24 \text{ cfu}/\text{m}^3$ around the right axilla, $42.7 \pm 38.8 \text{ cfu}/\text{m}^3$ around the left axilla and 45.1 ± 39.8 around the forced-air blower.

Fungal contamination was uncommon; *C. parapsilosis* was found on the non-disinfected skin of one patient, and *Aspergillus flavus* was found in the air rising around the axilla of another subject.

All the subjects in this study had an uncomplicated postoperative course, free from surgical wound infection, and from systemic complications such as cystitis or bronchopneumonia.

Discussion

Lee et al. demonstrated that measurements from different active air samplers may not be directly comparable, despite a comparison of three sampling devices, collecting simultaneous samples, showing high linear correlations between methods.²⁴ The same evidence is underlined in the CDC guidelines for environmental infection control in healthcare facilities.²⁵ Perioperative

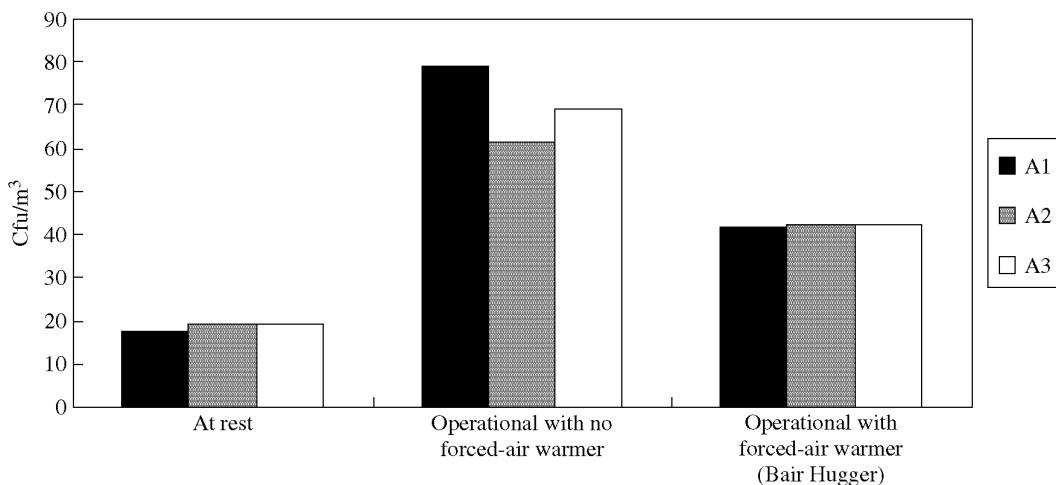


Figure 2 Mean bacterial load (cfu/m^3) in the three sampling points in at-rest and operational conditions and after placement of the forced-air blanket.

hypothermia is a common phenomenon, associated with physical factors such as exposure of patient to the operating theatre ventilation system and the infusion of cold solutions, but more importantly to anaesthesia-induced alterations on the individual's thermal homeostasis mechanisms.

Within the first hour of induction, both general and local anaesthetics act on the sympathetic system, inhibiting peripheral vasoconstriction and causing a redistribution of the heat from the body core to the periphery. In addition, the reflex shivering mechanism can be diminished, especially if there is associated administration of muscle relaxants.²⁶ The Bair Hugger blanket is considered to be among the most effective systems for achieving and maintaining a correct perioperative regulation of body heat.^{27,17,28} It exploits the active warming principle, transferring the warmth of the inner circulating heated air to the patient's body surface, by convection.⁹

The Bair Hugger is not indicated in surgical situations that cannot offer a sufficient skin-blanket coverage area to maintain adequate body heat, including liver transplantation, major abdominal surgery, patients with multiple trauma, etc.^{11,29} When it can be used, the system has the advantages of being non-invasive, cheap and simple to use, and above all effective. In our study, no patient developed any of the complications of hypothermia described in the literature, such as hypertension, myocardial ischemia, ventricular tachycardia, haemorrhage resulting from alterations of the platelet function and the activity of some enzymes involved in the clotting cascade, or local or general infections associated with cold-induced skin vasoconstriction.^{1,2,30} The latter induces a reduced

oxygen tension in subcutaneous tissues, rendering them more susceptible to microbial invasion and to neutrophil oxidation-induced inhibition of lymphocyte antibody formation and killing functions.³

The role of the forced-air body blanket as a potential source of infection is still controversial. Avidan *et al.* demonstrated a higher airborne bacterial load in the air samples analysed, and a higher incidence of nosocomial infections in patients kept warm using the Bair Hugger.¹² More recent studies, however, have not found a significant increase in the bacterial load in the operating theatre attributable to use of the system,¹³ whereas other studies that did report such an increased bacterial load did not find an associated significant increase in the frequency of nosocomial infections.³¹

The results of this study seem to point to the same conclusion. In none of the surgical patients did a nosocomial infection develop. Although a significantly increased bacterial load was recorded both after the patient's entry into the operating theatre ($P < 0.001$) and after placement of the body-warming system at all the sampling points, not one patient in this study developed a nosocomial infection. There was also a statistically significant difference in airborne bacterial load during operations in which the blanket was or was not used. In any case, in two of the sampling points (A2 and A3) no significant differences ($P > 0.05$) were observed between the two increases, although the mean bacterial load was numerically lower (Figure 2) after application of the Bair Hugger than immediately after placement of the patient on the operating table. Indeed, at sampling point A1, the increase in the bacterial load seemed to be significantly lower ($P < 0.05$)

between the moment in which the patient was placed on the operating table and after use of the body-warming system.

In light of the results reported here, the Bair Hugger system does not seem to pose a real risk of nosocomial infections, while it does offer the advantage of preventing the potentially grave consequences induced by hypothermia during major orthopaedic surgical procedures. The increased bacterial load found after application of a body-warming system appears to be comparable to, or lower than, the load present at the time of placement of the patient on the operating table. This provides further confirmation of the literature data supporting the contention that the main potential contamination factor in the operating theatre is the presence of the theatre medical staff themselves, their movements, and in general their behaviour.

Our study has some limitations. The sample size of patients was small for the calculation of the statistical incidence of surgical site infection after the use of the Bair Hugger. Further studies are needed to determine the security of this active warming system. Besides, it is evident that the operating theatre personnel themselves play an active role in introducing potential nosocomial pathogens into the environment. This variable is not easily quantifiable.

Conflict of interest statement

None declared.

Funding source

University of Bari.

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